OXIDATIVE STRESS AND ALTERATIONS OF SIGNAL TRANSDUCTION DEFICITS IN AGING AND AGE-RELATED DISEASE J. Joseph, R. Villalobos-Molina, S. Erat, J. Strain USDA-ARS Human Nutrition Research Center, Boston, MA 02111

For 40 years, the free radical hypothesis of aging has been invoked to suggest that age-related changes occur as a result of an increasing inability to cope with oxidative stressors. In the brain, evidence suggesting that free radicals may contribute to decreased function in normal aging is still controversial. Our research has focussed on studying possible relationships between functional, age- behaviorally-related neuronal deficits and oxidative stress. One such index is the loss of sensitivity that occurs in several receptor systems as a function of age. This loss occurs partially as a result of altered signal transduction (ST). Assessments have involved determining the nature of age-related reductions in oxotremorine enhancement of K^+-evoked dopamine release (K^+-ERDA) from superfused striatal slices. Using this model we have found that: a) Reductions can be restored with in vivo and in vitro administration of the free - radical trapping agent, N-tert-butyl-α-phenylnitrone (PBN); b) Decrements in DA release induced by NO or H_2O_2 from striatal slices from both young and old animals could be restored with α-tocopherol or PBN; c)ST decrements, such as those seen in aging, could be induced with radiation exposure; d) Pre-incubation of the striatal slices with cholesterol decreased subsequente deleterious effects NO or OH^- on DA release. Thus, cholesterol, which increases in neuronal membranes as a function of age, may function as a potent antioxidant and protectant, against neuronal damage. These results suggest that therapeutic efforts to restore cognitive deficits in aging and age-related disease might begin with antioxidant reversal of ST decrements.